

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**

**IN RE: Acetaminophen – ASD-ADHD
Products Liability Litigation**

22md3043 (DLC)

This Document Related To: All Cases

**MEMORANDUM IN OPPOSITION TO DEFENDANTS' RULE 702 MOTIONS
TO EXCLUDE DR. BRANDON PEARSON**

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PRELIMINARY STATEMENT

Acetaminophen (APAP) is far too dangerous to ethically commission a study of its biological effects on pregnant women and their unborn children. So conscientious scientists study it “preclinically” in animals, cell cultures, and computationally. Peer-reviewed preclinical study after peer-reviewed preclinical study shows that APAP causes biochemical reactions that are plausibly linked to autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). That is why a long list of first-rate scientists identify these reactions as plausible biological mechanisms that can disrupt prenatal neurodevelopment. [REDACTED]

[REDACTED]. Here, it fantastically claims that Dr. Pearson should have ignored it entirely. Dr. Pearson agrees [REDACTED]. So does Rule 702.

Dr. Pearson’s report carefully identifies and reviews several lines of evidence—including in vivo (animal), in vitro (cell-culture), and in silico (computational)—demonstrating APAP’s toxic effects on neurodevelopment. After transparently evaluating the relevant studies and explaining the weight he assigned the lines of evidence, Dr. Pearson concludes that prenatal APAP exposure can cause ASD and ADHD in offspring through several APAP-induced biochemical changes. These include the same mechanisms identified by numerous independent scientists: oxidative stress (through the development of a compound called NAPQI), epigenetic changes, effects on the endocannabinoid system, effects on the Brain-Derived Neurotrophic Factor (“BDNF”), effects on serotonergic signaling, and effects on prostaglandins. *See* Ex. 193, Bauer (2021), at 760, 763 & n.145.

Defendants seek to brand all these mechanisms “wildly speculative.” Defs. Mech. Br. at 1, Dkt. 1165. And on Defendants’ telling, that will remain true always and forever. Their tactical

nihilism reduces to the false claim that preclinical evidence is never relevant to assess APAP's effect on humans, that only human studies fit the bill, and yet that human studies are impossible due to ethical constraints. *See* Ex. 120, Kuffner Dep. Tr. at 187:9–190:1. Rule 702 does not declare that reasonable scientists must follow Defendants' philosophically bankrupt version of epistemology. Outside of litigation, scientists do not practice it.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] It is for a jury to decide whether Dr. Pearson's contrary opinion, reached through his own rigorous, well-grounded weight-of-the-evidence analysis, is more persuasive. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 596 (1993). Opinions do not morph from "wildly speculative" to inarguably correct depending on which party they happen to support. Defendants' Rule 702 Motions to exclude Dr. Pearson's testimony should be denied.

BACKGROUND

I. DR. PEARSON'S QUALIFICATIONS

Dr. Pearson is a professor at Columbia University, where he is lab director of the Columbia Center for Children's Environmental Health, one of the world's leading centers for studying the effects of prenatal exposures on neurodevelopment. Long before he was retained by Plaintiffs, Dr. Pearson's research specifically studied mechanisms by which APAP affects neurodevelopment. At Columbia, which has an entire facility dedicated to studying nervous-system disorders through behavioral tests on mice, he has led studies that expose mice to prenatal and early-postnatal doses of APAP in order to model the neurodevelopmental effects from similar exposures in humans, including APAP's effects on gene expression. *See* Ex. 2, Rule 26 Expert Report of Brandon Pearson, MS, Ph.D. ("Pearson Rep."), Ex. A (CV as of June 7, 2023); *id.* at 1–3 (describing qualifications). Defendants do not contest Dr. Pearson's qualifications.

II. DR. PEARSON'S OPINIONS

Dr. Pearson's report assesses the published preclinical studies of APAP's effect on neurodevelopment, applying his expertise in conducting and reviewing such studies to determine whether they support the hypothesis that prenatal APAP exposure causes ASD and ADHD—and if so, how. Using a weight-of-evidence methodology drawn from published guidance documents, including principles from the Organisation for Economic Co-operation and Development (OECD) [REDACTED], Dr. Pearson explains how he collected and filtered for studies relevant to the inquiry. *See* Ex. 2, Pearson Rep., at 67–72. That evidence—including 15 rat studies, 9 mouse studies, and 8 in vitro/ex utero studies—were then analyzed in depth, receiving both a numerical score reflecting the strength of the study's design and a thorough narrative

analysis that describes the studies’ findings, strengths and limitations. *See id.* at 72–82 (weighting standards); *id.* at 82–128 (weight-of-evidence review of preclinical evidence).

Dr. Pearson weighted the findings within each line of evidence. He concluded that the preclinical evidence as a whole shows that prenatal APAP exposure is capable of causing ASD and ADHD by disturbing normal neurodevelopmental processes through several independent mechanisms. *Id.* at 127–28.

III. THE IDENTIFIED MECHANISMS OF ACTION

Dr. Pearson opines on biological plausibility: “a judgment about whether an agent *plausibly could cause* a disease, based on *existing knowledge* about human biology and disease pathology.” *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 181 (S.D.N.Y. 2009) (emphases added). Biological plausibility is one of the nine factors that Sir Austin Bradford Hill identified as probative of general causation. *See id.* at 187 (listing categories). This factor “takes into account data that is helpful in understanding *how* the risk factor produces the disease,” that is, the mechanism of action. *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17 CV 4188, 2021 WL 4037820, at *9 (S.D.N.Y. Sept. 3, 2021) (emphasis added; quotation marks omitted).

A plausible mechanism of action consists of a biological change that (1) can be induced by prenatal exposure to APAP and (2) can in turn contribute to the development of ASD and ADHD in offspring. Dr. Pearson identifies several such mechanisms that are grounded in existing knowledge of human biology and ASD/ADHD pathology.

A. The Identified Mechanisms Are Grounded in Existing Scientific Knowledge.

Plaintiffs’ experts identify several changes that APAP exposure is known to induce in the body and that are known to raise the risk of ASD and ADHD in offspring. Dr. Pearson’s report

explains the chemistry underlying these biological mechanisms. The following is an overview of those mechanisms, tracking the order in which Dr. Pearson discusses them.

i. NAPQI and Oxidative Stress.

When APAP is metabolized, 5–10% is converted into the molecule N-acetyl-p-benzoquinone imine (“NAPQI”) through an enzyme known as CYP2E1. Dr. Pearson’s report has an illustration of the process [REDACTED]



[REDACTED] NAPQI is a “pro-oxidant,” also known as a “free radical”—a molecule that is naturally produced during metabolism but that can cause cell damage. A healthy body maintains a balance between free radicals and antioxidants, which neutralize the free radicals. When free radicals exceed the body’s ability to detoxify them through antioxidants, the body experiences oxidative stress. *See id.* at 51–60 (discussing NAPQI and oxidative stress as mechanisms of action).

It has been known since the 1970s that APAP can cause oxidative stress. *See* Ex. 3, Expert Report of Robert M. Cabrera, Ph.D. (“Cabrera Rep.”), at 38–39. Once ingested, APAP is primarily metabolized in the liver. After the CYP2E1 enzyme converts some of the APAP into NAPQI, the NAPQI is detoxified by an antioxidant called glutathione (GSH). But prolonged oxidative stress—

i.e., imbalance between NAPQI and glutathione—can deplete glutathione levels, allow NAPQI to accumulate, and leave the body vulnerable to NAPQI’s toxic effects. Although Defendants refer to NAPQI as a “minor metabolite,” Defs. Mech. Br. at 2, APAP-induced oxidative stress as a result of NAPQI is a leading cause of acute liver failure in the United States. *See* Ex. 2, Pearson Rep., at 9–10. APAP overdose is currently treated with N-acetylcysteine (NAC), an antioxidant which helps the body neutralize NAPQI’s toxic oxidative effects. *See* Ex. 2, Pearson Rep., at 9–10; Ex. 3, Cabrera Rep., at 30–31; *see also* Ex. 30, Powell Dep. Tr. at 217:1–217:7 (Defendants’ expert Dr. Powell testifying that an APAP-containing product also contains antioxidants “[p]resumably to protect the liver from damage”).

APAP exposure can also cause oxidative stress in the fetal brain during neurodevelopment. The CYP2E1 enzyme that metabolizes some APAP into NAPQI is also found in the human fetal brain, and it is found there as early as the second trimester of pregnancy. *See* Ex. 2, Pearson Rep., at 52. Oxidative stress can cause several harmful reactions. It can damage developing neurons and their supporting cells, and alter their normal path of differentiation, proliferation and migration. It can cause inflammation in the brain, leading to further cell damage and prolonged oxidative stress. It can damage mitochondria, energy-producing organelles within cells, which are particularly critical within the energy-intensive developing brain. It can cause cell death, which can impair learning and memory, among several other impairments that are symptoms of ASD and ADHD. *See id.* at 50–54. The depletion of glutathione, an important antioxidant which is already depleted in pregnant mothers, can itself cause further damage by rendering the developing brain helpless in the face of otherwise tolerable oxidative exposures.

Multiple studies have demonstrated the link between oxidative stress and ASD/ADHD. As one just one example, studies have repeatedly found that brain tissue in people with ASD and

ADHD reflect higher levels of oxidative stress as compared to neurotypical individuals. *See id.* at 53 (collecting studies); Ex. 7, Rule 26 Rebuttal Expert Report of Brandon Pearson, MS, PhD, at 8 (“Pearson Rebuttal Rep.”) (additional studies). Along with causing oxidative stress, NAPQI can have toxic effects of its own. The overabundance of a free radical like NAPQI is dangerous to DNA, and NAPQI can cause DNA damage by, for example, inhibiting enzymes that prevent DNA from becoming tangled.¹ As explained in Dr. Pearson’s report, the delicate processes underlying normal human neurodevelopment require that molecules in the brain, including DNA, function normally in order to ensure that brain cells and their networks develop appropriately. Indeed, researchers have found “patches of disorganization” in the brains of people with ASD. Ex. 121, Stoner (2014), at 1209 (discussed in Ex. 2, Pearson Rep., at 25).

ii. Epigenetic Changes.

Epigenetics refers to how chemical compounds affect gene expression without changing the underlying DNA—colloquially, by turning certain genes “on” or “off.” Abnormal epigenetic changes during neurodevelopment can lead to abnormal gene expression and thereby to disorders like ASD and ADHD. That genetic changes can contribute to these disorders is common ground: Defendants’ experts testify that ASD and ADHD result from genetic mutations, though they disregard the role of environmental exposures, such as APAP and other drugs taken during pregnancy, in that process.

Prenatal APAP exposure affects the expression of genes associated with ASD and ADHD. *See* Ex. 2, Pearson Rep., at 60–61 (discussing epigenetic changes as mechanisms of action).

¹Defendants are simply incorrect that Dr. Pearson’s report provides “very little explanation” of how “acetaminophen can damage DNA itself in a way that could cause some sort of neurodevelopmental disorder.” Defs. Mech. Br. at 34 n.50. Dr. Pearson provides a clear graphic depiction of the biological pathway from APAP exposure to DNA damage, *see* Ex. 2, Pearson Rep., at 55 fig.28, then devotes an entire section to explaining how that damage can occur and lead to neurodevelopmental disorders, including ASD and ADHD, *see id.* at 57–60. That section cites several studies in addition to the Bender study that Defendants, with very little explanation, reject for being an *in vitro* study.

In fact, researchers have found that APAP is among the medications that affect the most ASD-associated genes. *See* Ex. 1, Expert Report of Andrea Baccarelli, MD, PhD, MPH (“Baccarelli Rep.”), at 49–51. Multiple studies have specifically found that prenatal APAP exposure can affect DNA methylation, an epigenetic process where a particular chemical group (a “methyl” group) is added to DNA. Changes to this process can affect neurotransmission (the transfer of information between brain neurons) and other essential brain functions, and abnormal changes have been found to lead to neurodevelopmental disorders, including ASD and ADHD.

iii. Effects on the Endocannabinoid System.

The endocannabinoid system consists of signaling molecules (endocannabinoids), receptors for those molecules, and enzymes that act on those molecules. Located throughout the nervous system, the endocannabinoid system sends signals to all parts of the body, providing a bridge between the body and mind. Normal functioning of this system is essential to neurodevelopment; dysfunction can disrupt neurotransmission, among other brain functions, and further contribute to brain inflammation. That is why any doctor would caution a mother against ingesting cannabis (marijuana) while pregnant.² Endocannabinoid disruption has been specifically linked to ASD, while studies also support an association with ADHD. *See* Ex. 2, Pearson Rep., at 61–63 (discussing endocannabinoid effects as mechanisms of action).

APAP interacts with the endocannabinoid system; indeed, this interaction is considered a source of APAP’s analgesic effect. But this interaction can also cause endocannabinoid disruption during neurodevelopment. As Dr. Pearson explains in greater detail, an APAP metabolite, p-aminophenol (PAP), can disrupt key endocannabinoid enzymes. In the presence of one of these enzymes, this metabolite can also lead to the formation of a compound called AM404, which can

² Defendants question whether the causal link to ASD and ADHD is strong enough even for prenatal exposure to marijuana. *See* Defs. Mech. Br. at 31. The evidence speaks for itself.

in turn lead to abnormally high levels of a primary endocannabinoid (anandamide).³ ADHD patients have been found to have elevated anandamide in their plasma.

iv. Effects on Other Signal-Carrying Molecules (BDNF, Serotonins, and Prostaglandins).

APAP has also been found to disrupt multiple other signaling systems that are involved in neurodevelopment and, when disrupted, can contribute to the development of ASD and ADHD. *See* Ex. 2, Pearson Rep., at 63–66 (discussing effects on BDNF, serotonins, and prostaglandins as mechanisms of action).

BDNF is a type of protein molecule (known as a neurotrophin) that is widely present in the fetal brain and that supports the growth and functioning of neurons in the brain and nervous system, with particular importance to learning and memory. BDNF is released by brain cells and transmits signals that regulate several aspects of neurodevelopment, including neuron growth and differentiation. Disruptions to these signals have been observed to cause behavioral changes in test animals and have been linked with ASD and ADHD in humans. The preclinical studies examined in Dr. Pearson’s report also contains evidence of APAP-induced disruptions to BDNF. *See id.* at 90–91, 101–02.

Serotonin, a neurotransmitter, underlies another signaling system that is integral to various aspects of brain development. Like the link between APAP and the body’s endocannabinoid system, FDA has explicitly recognized APAP’s serotonergic effects. [REDACTED]

[REDACTED] Several studies have observed abnormal serotonin levels in people with ASD, and symptoms of both ASD and ADHD arise from abnormalities in brain functions that serotonin regulates during

³ In their effort to downplay APAP’s neurodevelopmental effects, Defendants refer to AM404, like NAPQI, as a “minor” APAP metabolite. Defs. Mech. Br. at 28. They never define that term, much less cite a source. Regardless, the developing brain is vulnerable even to “minor” perturbations. *See* Ex. 2, Pearson Rep., at 18–20.

neurodevelopment. Effects on BDNF and the endocannabinoid system, including through the APAP-induced compound AM404, can also impact serotonergic signaling. The preclinical studies examined in Dr. Pearson’s report contain further evidence of APAP-induced disruptions to serotonin function. *See* Ex. 2, Pearson Rep., at 86–90.

Finally, APAP inhibits the production of prostaglandins, fatty molecules with diverse functions throughout the body. This is one of APAP’s primary actions and another potential source of its fever-reducing effects. The brain has several prostaglandin receptors, and prostaglandins are present in the earliest stages of human development. They play many roles in neurodevelopment and are particularly important to the developing cerebellum, a part of the brain involved in many behaviors and functions—*e.g.*, motor control, executive functioning, and social interaction—that are frequently impaired as symptoms of ASD or ADHD. Researchers have accordingly found that exposure to prostaglandin inhibitors, including APAP, can disrupt neurodevelopment. And other APAP effects, including the production of AM404, can affect this signaling system as well.

B. The Identified Mechanisms Are Generally Recognized as Plausible.

At a 2022 meeting of the Science Advisory Board for the National Center for Toxicological Research, the current director of the FDA’s Division of Neurotoxicology, John Talpos, addressed, in his words, the “multiple mechanisms by which APAP may cause neurotoxicity.” Ex. 123, NCTR Science Advisory Board Meeting (“SAB Mtg.”), 36–37 (May 19, 2022). Homing in on “one potential mechanism” that had “popped out as lending itself to evaluation in a vitro setting,” he proceeded to offer a description of oxidative stress (in his words, “CYP2E1-mediated metabolism”) that closely tracks Dr. Pearson’s analysis:

CYP2E1, a lot of you probably know a lot about it, is highly expressed in the liver. *APAP metabolized by CYP2E1 will eventually deplete levels of glutathione, resulting in free radical formation and hepatotoxicity. While CYP2E1 is expressed on neurons in the human brain, it is at lower levels than in the liver, but it is still*

very much there. This raises the question if CYP2E1 mediated toxicity could occur at the brain. If so, this is potentially really problematic, as alcohol, halogenated anesthetics, and even a metabolite of caffeine are all metabolized by CYP2E1. *So there is real potential to push this system too far.*

Id. (emphases added). Far from dismissing this or any other potential mechanism of APAP's neurotoxicity as "wildly speculative," Defs. Mech. Br. at 1, Talpos noted that the FDA is *currently investigating* APAP's effect on neurodevelopment through oxidative stress. *See* Ex. 123, SAB Mtg., at 37 ("[T]his is a project that's being led by Dr. Shuliang Liu [an FDA visiting researcher]."). "And of course," he continued, tracking Dr. Pearson's own reasoning, "the developing brain is very vulnerable to all types of different abnormal energetic demands. While this project is still in development, our starting point will be to determine if neurons die after APAP exposure as a consequence of a CYP2E1 mediated mechanism." *Id.*

These remarks are part of a trend. Indeed, Defendants' own mechanism expert, Dr. Powell, has conceded that many of the mechanisms Plaintiffs' experts analyzed are at least plausible causes of neurodevelopmental disruption. *See, e.g.,* Ex. 2, Powell Tr. at 61:2–25 (acknowledging that oxidative stress can adversely affect neurodevelopment); *id.* at 72:8–14 (acknowledging that APAP can affect serotonergic signaling in the brain); *id.* at 74:1–5 (acknowledging that changes in gene expression can lead to pathologies). Defendants' expert Dr. Alexander Klevzon has likewise acknowledged these mechanisms, including in a textbook chapter he coauthored. *See* Ex. 98, *Textbook of Autism Spectrum Disorders* 191 (2d ed. 2022) ("Acetaminophen may interfere with endogenous hormones and signaling pathways in the developing fetus. It also has been suggested that acetaminophen increases the risk for ASD by causing neuronal oxidative stress.") (citations omitted); *see also* Ex. 28, Klevzon Dep. Tr. at 514:23–515:13.

[REDACTED]

[REDACTED]

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴ Dr. Pearson considered all the other studies referenced in this table but included in his weighting analysis only those that met his criteria for data relevance. *See* Ex. 2, Pearson Rep., at 69–72.

[REDACTED]

[REDACTED]

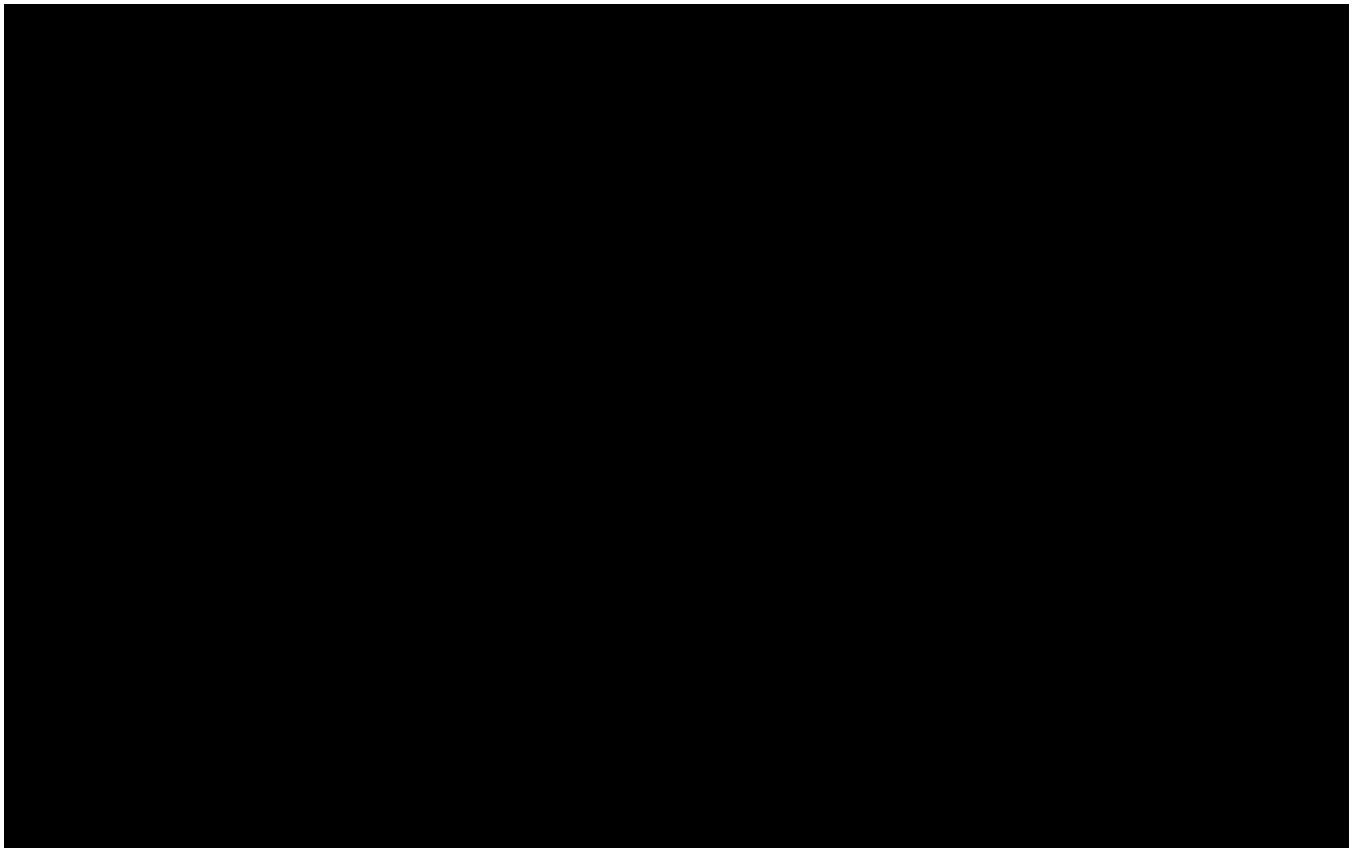
[REDACTED] Dr. Pearson's report focuses on APAP's developmental effects, though he considers endocrine effects where relevant to neurodevelopment. *See* Ex. 2, Pearson Rep., at 5.

[illegible]

6 [REDACTED]

David Michaels, former Assistant Secretary of Labor for OSHA and former Assistant Secretary of Energy for Environment, Safety and Health, stated as follows: “[h]aving cut their teeth manufacturing uncertainty for Big Tobacco, scientists at ChemRisk . . . and other consulting firms now battle the regulatory agencies on behalf of the manufactures of benzene, beryllium, chromium, MTBE (methyl tertiary-butyl ether), perchlorates, phthalates, and virtually every other toxic chemical in the news today. Their business model is straightforward. They profit by helping corporations minimize public health and environmental protection and fight claims of injury and illness.” Ex. 134, Michaels (2008) at 46.

[illegible]



ARGUMENT⁷

Dr. Pearson identifies multiple, scientifically grounded mechanisms by which APAP may cause ASD and ADHD. They are all plausible. They all have independent support in the peer-reviewed literature. [REDACTED]. At a minimum, a reasonable scientist could testify that these mechanisms are plausibly at work. Defendants’ cry of “wildly speculative,” Defs. Mech. Br. at 1, does not change the analysis.

⁷ Plaintiffs refer the Court to the Rule 702 legal standard set forth in Plaintiffs’ Opposition to Defendants’ Motions To Exclude Dr. Andrea Baccarelli at 33–34.

I. THE PLAUSIBLE BIOLOGICAL MECHANISMS IDENTIFIED IN DR. PEARSON’S REPORT SUPPLY INDEPENDENT EVIDENCE OF CAUSATION.

Defendants’ efforts to rewrite standards in their favor begins with the causation standard itself. Defendants first assert that “[b]iological plausibility is *necessary*—but not sufficient—to establish general causation.” Defs. Mech. Br. at 1 (emphasis added). They next urge the Court to redefine “plausible” to mean “proven.” *Id.* at 12 (quoting *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295-96 (M.D. Fla. 2007)). The law clearly rejects both maneuvers. Showing a biologically plausible mechanism strongly supports a causal inference, but it is not necessary to draw one; and as Defendants’ expert Dr. Jennifer Pinto-Martin rightly conceded, plausible means “possible,” not proven.

On the first point, Bradford Hill explained it best: “[i]t will be *helpful* if the causation we suspect is biologically plausible. But this is a feature I am convinced we *cannot demand*.” Ex. 69, Bradford Hill Address, at 298 (1965) (emphasis added). After all, there had been “no biological knowledge to support (or to refute) Pott’s observation in the 18th century of the excess of cancer in chimney sweeps,” a famous early recognition of an environmental carcinogen. *Id.* By the mid-twentieth century, Bradford Hill himself did not know the exact biological mechanism by which cigarette smoking caused lung cancer. Yet he and the rest of the world were still able to conclude, based on observational studies, that it did. *See id.* at 295-96. To the extent relevant, Defendants’ out-of-circuit caselaw remains in accord with what Bradford Hill clearly said. *E.g.*, *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1356 (S.D. Fla. 2011) (“When [mechanistic evidence] is present it can greatly strengthen a causal inference, but when it is absent it does not necessarily undermine the inference.”) (quotation marks omitted).

Plausible also means exactly what the dictionary reports: possible or credible, not conclusively proven. *See* Ex. 25, Pinto-Martin Dep. Tr. at 542:22–543:3; *In re Fosamax*, 645 F. Supp. 2d at 183 (“That the mechanism remains unknown does not mean that the one proposed by the [plaintiffs’] experts is not widely accepted as plausible. The Court finds that the existence of a biologically plausible mechanism bolsters the reliability of the proffered opinions on causation. However, this mechanism should not be represented as a matter of scientific certainty.”) (citations omitted); *In re Pfizer Inc. Secs. Litig.*, Nos. 04 Civ. 9866, 05 md 1688, 2010 WL 1047618 at *6 (S.D.N.Y. Mar. 29, 2010) (allowing expert mechanism testimony where mechanism was “deemed plausible and credible in the relevant medical literature” and noting that the testimony, “while about a mechanism not proven conclusively or uniformly accepted, is far from baseless speculation”); *see also Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 25 (1st Cir. 2011) (“The district court also erred in its apprehension of the scientific concept of biological plausibility and its place in Dr. Smith’s analysis. The concept of biological plausibility, which numbers among the nine Hill viewpoints, asks whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent.”).

Defendants’ motion is written to give the false impression that Dr. Pearson’s proposed mechanisms are hypothesized for the first time in his expert report. He is hardly the first to opine that these identified mechanisms “plausibly could cause” ASD and ADHD. *In re Fosamax*, 645 F. Supp. 2d at 181. Independent scientists from the Consensus Statement’s signatories to the upper ranks of FDA all share Dr. Pearson’s opinion, as seen above. The *Daubert* standard replaced “the bright-line ‘general acceptance’ test” that courts had previously applied to expert testimony, and the Court’s task now is simply to “ensur[e] that an expert’s testimony both rests on a reliable

foundation and is relevant to the task at hand.” *Amorgianos v. Nat’l R.R. Passenger Corp.*, 303 F.3d 256, 265 (2d Cir. 2002) (quotation marks omitted). But the Court can proceed with confidence that Dr. Pearson’s testimony rests on a sturdy foundation because his opinions are shared by scientific peers outside of litigation.

II. DR. PEARSON HAS RELIABLY ASSESSED WHETHER PRENATAL APAP EXPOSURE CAUSES ASD OR ADHD THROUGH THE IDENTIFIED MECHANISMS.

The *actual* question here is whether Dr. Pearson reached his conclusions through reliable methods. On that dispositive issue, Defendants have comparatively little to say. *See* Defs. Mech. Br. at 17–21. Where an expert applies reliable methods with the same rigor he brings to his daily work, his conclusions cannot be “the sort of ‘junk science’ with which *Daubert* was concerned” even if other scientists could disagree with those conclusions. *Daniels-Feasel*, 2021 WL 4037820, at *6 (quotation marks omitted). Dr. Pearson’s methodology is both reliable and reliably applied.

A. Dr. Pearson’s Weight-of-Evidence Methodology Is Reliable.

“Courts have found that the weight of the evidence methodology is scientifically acceptable because it is not intrinsically unscientific for experienced professionals to arrive at a conclusion by weighing all available scientific evidence.” *Id.* (cleaned up). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] the exact same framework that largely informed the WoE methodology in Dr. Pearson’s report, *see* Ex. 2, Pearson Rep., at 5–6.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Ex. 2,

Pearson Rep., at 80 (noting that “[a] qualitative approach is generally used to describe the weight of a particular [line of evidence],” and citing OECD guidance). Different scientists can make different qualitative judgments, as Dr. Pearson [REDACTED] But Dr. Pearson’s report does not fail *Daubert* simply because Defendants disagree with his judgment. What matters is whether is underlying methodology was itself reliable. It indisputably was.

B. Dr. Pearson Reliably Applied His Weight-of-Evidence Methodology.

With no ground to challenge Dr. Pearson’s methodology, Defendants purport to challenge the way he applied it. This challenge amounts to repeated accusations of cherry-picking. These accusations are implausible on their face.⁸ Dr. Pearson’s report thoroughly reviews the relevant preclinical literature, [REDACTED] His report indicates whether particular studies weigh in favor of or against the hypothesis that prenatal APAP exposure can cause ASD or ADHD, assigning positive or negative scores respectively. And Dr. Pearson explains those assessments with narratives about each study highlighting both qualitative strengths and weaknesses. This is all clear from the face of the report—including the scales that visually depict the relative weight of each study within a line of evidence. *See* Ex. 2, Pearson Rep., at 99 (depicting overall weight of rat studies, where 15 studies weigh in favor of casual hypothesis to varying degrees); *id.* at 115 (overall weight of mouse studies, where 7 studies weigh in favor of causal hypothesis and 2 studies weigh against casual hypothesis to varying degrees); *id.* at 123 (overall weight of in vitro/ex utero studies, where 5 studies weigh in favor of causal hypothesis and 3 studies weigh against causal hypothesis to varying degrees). This thorough and transparent analysis will allow the factfinder to test Dr. Pearson’s conclusions and to reach its own. That is precisely the sort of expert testimony *Daubert* allows.⁹

Defendants chastise Dr. Pearson for supposedly ignoring *one* study, Blecharz-Klin (2014), that failed to find an effect on certain amino acids in the hippocampus, which, as Dr. Pearson’s

⁸ Defendants seemingly lodged the same, empty accusations of “cherry-picking” against all Plaintiffs’ experts without regard to each expert’s underlying methodology and analysis. For instance, Defendants criticize Dr. Pearson for failing to address Gustavson (2021), but that is an epidemiological study and Dr. Pearson clearly only assessed the preclinical evidence. *See* Defs. ADHD Br. at 27, Dkt. 1162.

⁹ To put it into perspective, Defendants’ expert Dr. Powell fully describes and analyzes only two of the ninety-nine studies identified in his literature search—Saad (2016) and Baker (2023), *see* Ex. 2, Powell Rep., ¶¶ 67–70—and otherwise purports to identify the “[c]ritical [f]laws” that undermine the “[r]emaining [p]ublications” primarily through string citations to end notes that reference the other ninety-seven studies. *Id.* at 33; Ex. 30, Powell Dep. Tr.

report notes, Blecharz-Klin later found in a 2017 study. *See* Defs. Mech. Br. at 19. The 2014 study, however, involved APAP treatment on *adult* rats, unlike the 2017 study. Dr. Pearson therefore did not “ignore” this study, but chose not to *weigh* it because it was not relevant to whether *prenatal* APAP exposure contributes to ASD or ADHD. Defendants also assert that Dr. Pearson “goes so far as to claim that two studies, one showing that a treatment increased levels of a chemical and one showing that the same treatment decreased levels of a chemical, could be deemed consistent because both show a change.” Defs. Mech. Br. at 20. True, he does. Defendants seem to think this undermines Dr. Pearson’s methodology. It instead simply undermines Defendants’ scientific credibility.

As Dr. Pearson explained, toxicants like APAP can affect different parts of the developing brain in different ways and at different times. *See* Ex. 2, Pearson Rep., at 127 (“Though individual studies may show mixed or bidirectional results, neurodevelopmental perturbation of prenatal APAP can manifest in various ways in terms of directionality.”). A toxicant might initially cause a certain neurochemical to decrease, leading the brain to respond by synthesizing more. Depending on the time at which a measurement is taken, then, a test might show a decrease or an increase as the body attempts to maintain homeostasis. But the measurement in both tests will still be showing a response to the toxicant. *See* Ex. 131, Tyl (2008), at 353 (“Several important response patterns include . . . paradoxical dose response curves (e.g., U-shaped).”); *accord* Ex. 7, Pearson Rebuttal Rep., at 4 (“[F]indings that are in the opposite direction of the prediction nevertheless demonstrate that the sensitive neurobehavioral system is perturbed by the developmental exposure to the medication.”).

at 86:11-16. But he provides no objective or transparent means to test that analysis. In order to understand his analysis of the remaining publications, Dr. Powell testified: “I expect someone who is replicating what I’ve done to read the papers and decide for themselves what they feel is relevant.” Ex. 30, Powell Dep. Tr. at 107:2–18.

It is therefore unscientific to insist, as Defendants do, on the same “direction” of findings within or across studies before any findings can be considered consistent toxicological evidence of causation within a WoE analysis. The point is explained in the guidance literature on which Dr. Pearson relied. *See* Ex. 7, Pearson Rebuttal Rep., at 4 (“Since different functional domains are evaluated by different tests in the study, a complete concordance of effects is not expected and/or necessary to establish the relevance and/or validity of a finding.”) (quotation marks omitted).¹⁰

Another guidance document puts the point in even plainer terms:

Neurotoxic adverse effects are defined as *any change* in the structure or function of the central and/or peripheral nervous system. This includes alterations in *either direction* (i.e., increases or decreases) from baseline or normal conditions as well as effects that are transient, occur only at specific times during development, or appear as changes in the ontogeny of developmental processes.

Ex. 132, NAFTA, DNT Guidance Doc. at A-9 (emphases added). If a toxicant did not affect neurodevelopment at all, no change would be observed in any direction. When assessing whether a toxicant can affect neurodevelopmental processes, therefore, a study is relevant if it shows an effect on those processes. The direction of the effect is certainly relevant information, but it does not preclude a study from adding to the weight of causation evidence, let alone from even being considered in a WoE analysis. Determining whether an effect is consistent with the effects found in other tests, and thus whether the evidence supports a causal hypothesis, is what weighing the evidence is for. It is thus Defendants who present an unscientific “final picture,” *In re Rezulin*

¹⁰ Dr. Pearson draws this quote from the Ex. 131, Tyl (2008) guidance. Defendants respond that this “paper does not stand for the proposition that a scientist can reach a causal conclusion based on non-replicated data.” Defs.’ Mech. Br. at 18 n.4. But that is no response. Dr. Pearson does not cite this guidance for that proposition. Meanwhile, Defendants cite no guidance for the contrary proposition that a causal conclusion can be based only on data that satisfies Defendants’ narrow idea of replication. *See infra* Argument Part III.C. Defendants eventually admit that this guidance simply “calls for careful weighing of any potentially inconsistent results.” Defs.’ Mech. Br. at 18 n.4. That is what Dr. Pearson’s report does.

Prods. Liab. Litig. (MDL No. 1348), 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004), by seeking to dismiss findings based on supposed differences in “direction” regardless of context.

Consider the Blecharz-Klin 2015 and 2016 studies that Defendants attempt to portray as inconsistent. *See* Defs. Mech. Br. at 19–20. One study found that rats exposed to APAP during development had lower MHPG (a metabolite) in the spinal cord, while another found that exposed rats had higher MHPG in the brain cerebellum. Yet the brain and spinal cord are individual parts of the central nervous system, and, as such, are capable of individual responses to toxins. Taken together, these studies show that prenatal APAP exposure affects metabolism throughout the central nervous system. Of course, that alone is not *determinative* evidence that prenatal APAP exposure leads to ASD or ADHD. But that is why a WoE analysis must take into account the totality of the evidence of a toxicant’s effects on neurochemistry.

Dr. Pearson’s report fully acknowledges the diversity of findings across preclinical studies, including the Blecharz-Klin 2015 and 2016 studies. *See* Ex. 2, Pearson Rep., at 87 (noting the “significantly lower levels of MHPG” in rat spinal cords in the 2015 study); *id.* at 88 (noting the “significantly higher cerebellar concentration of . . . MHPG”). Rather than waving them away, he concludes that “[t]he heterogeneity of ultimate endpoints seen in the preclinical studies described in [his] report *makes sense* given the context of the extremely delicate cascading cellular processes disturbed by APAP use.” Ex. 2, Pearson Rep., at 127 (emphasis added). That conclusion is grounded in the nature of APAP toxicity, in ASD/ADHD etiology, and in standard practices of assessing developmental-neurotoxicology studies. Defendants’ disagreement with that conclusion is no basis to exclude it.

The same goes for Defendants’ related accusation that Dr. Pearson unduly relies on “isolated findings” of causation when other findings in the same study might “show no association

with acetaminophen.” Defs. Mech. Br. at 20. Defendants offer no support for the proposition that particular findings cannot weigh toward causation simply because other tests in a study did not find a causal association. Nor could they. It is a basic statistical principle that null findings (*i.e.*, no causal association was observed) do not support the *opposite* conclusion (*i.e.*, no causal association *could* be observed). “Absence of evidence is not the same as evidence of absence.” Ex. 133, Leppink (2017), at 117. If a toxicology study finds no statistically significant effect on a particular endpoint, that finding does not suggest that the toxicant is incapable of exerting that effect. To be sure, positive findings might themselves result from chance. That is the reason for null-hypothesis testing within particular studies. Under the standard p-value of 0.05, one would expect to see a positive result 5% of the time due to random chance. In other words, if the null hypothesis were true and there were no causal association, there would still be a 5% chance of Type 1 error (false-positive finding). But APAP has been found to affect neurodevelopmental endpoints across *dozens* of tests, and Defendants make no effort to show how a significant portion of these findings could be the result of random chance.

In addition, the authors of those studies took great pains to use statistical techniques to control for spurious findings. Defendants point to three examples: a Blecharz-Klin (2015) study, the Blecharz-Klin (2017) study, and the Saeedan (2018) study. Defendants assert that these studies, which tested APAP’s effect on several developmental endpoints, failed to control for the possibility that some tests would yield false positive results by virtue of the number of tests run. *See* Defs. Mech. Br. at 20, 24. Defendants are simply incorrect. All these studies conducted relatively conservative statistical corrections. *See* Ex. 135, Blecharz-Klin (2015), at 135 (explaining statistical analysis conducted through the ANOVA method and two post-hoc tests: the Newman-Keuls test and Fisher’s Exact Test); Ex. 136, Blecharz-Klin (2017), at 8 (statistical

analysis conducted through the ANOVA method and Newman-Keuls and Duncan post-hoc tests); Ex. 137, Saeedan (2018), at 955 (statistical analysis conducted through the ANOVA method and the Newman-Keuls post-hoc test); *see generally* Ex. 138, Lee & Lee (2018) (explaining these and other types of corrections for multiple comparisons). Indeed, the Saeedan study was one of the (many) studies that Defendants' expert Dr. Powell belatedly realized *did* correct for multiple comparisons, forcing him to remove it in his amended report from the string-cite of studies he dismissed for purportedly failing to run that correction. *See* Ex. 139, Powell Redline Rep., ¶¶ 72, 91(d); Ex. 30, Powell Dep. Tr. at 95:9–97:3. His failure to similarly remove the Blecharz-Klin studies shows only the unreliability of his report.

Defendants would no doubt prefer that all studies of their product's neurodevelopmental effects, regardless of those studies' other characteristics, conduct statistical corrections so strict that they thereby run a significant risk of false *negatives*, *i.e.*, failure to see an effect where one exists. There is no support for that view, certainly not when human health is at issue. Researchers select statistical corrections that, in light of a study's sample size and other features, best balance the risk of false positives and false negatives. *See* Ex. 138, Lee & Lee at 353, 360. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In short, the many findings underlying Dr. Pearson's opinion cannot simply be dismissed as so many spurious associations. Nor does any guidance suggest, as Defendants do, that a separate

statistical-significance test must be run across studies in a WoE analysis.¹¹ Defendants’ expert Dr. Powell did not do so in his own purported weight-of-evidence review of the preclinical literature. And Dr. Pearson (unlike Dr. Powell) thoroughly evaluated the quality of all these studies, in keeping with the WoE guidance. *See* Ex. 141, OECD (2019), at 19 (“[T]he majority of chemical risk assessments conducted for commercial chemicals typically involve a qualitative approach to uncertainty analysis . . . simply because of the lack of adequate data to support statistical methods.”). These are peer-reviewed studies. Other scientists have already interrogated their statistical testing and deemed them worthy of publication. They provide reliable evidence of APAP’s causal relationship to the development of ASD and ADHD.

III. DEFENDANTS’ REMAINING ARGUMENTS ARE NOT *DAUBERT* ARGUMENTS.

Defendants’ remaining arguments are aimed at Dr. Pearson’s conclusions, not his methods. Three of these arguments call for broadly disregarding the existing preclinical evidence and any mechanism conclusions therefrom. The rest are attempts to nitpick certain studies. Even if valid, these arguments would go only to the weight of Dr. Pearson’s conclusion, not their admissibility. *See Amorgianos*, 303 F.3d at 267. And none are valid in any event.

A. Plausible Causal Mechanisms Can Be Identified for Complex Disorders like ASD and ADHD.

Defendants argue that Dr. Pearson cannot testify that prenatal APAP exposure causes ASD or ADHD through any biological mechanism because no scientist has “identified any process or biological pathway through which ASD or ADHD generally develops.” Defs. Mech. Br. at 12.

¹¹ Dr. Pearson did not somehow object to testing for statistical significance as “over-rigorous” in and of itself. Defs. Mech. Br. at 21. Defendants lift that quote from his discussion of the Saad (2016) study, which, as Dr. Pearson explains, found results consistent with APAP’s effect on neurodevelopment but negated its own findings by applying an inexplicably high threshold for statistical significance—requiring less than 0.8% likelihood of chance results rather than the standard 5%. *See* Ex. 2, Pearson Rep., at 102–05.

Without knowing “the precise pathogenesis of a condition,” Defendants contend, an expert cannot determine how a drug might contribute to that condition. *Id.* This argument is not just wrong. It is disingenuous. It turns on conflating the general with the more specific.

The lynchpin of Defendants’ case proves the point. They maintain, wrongly, that genetics are the exclusive cause of ASD and ADHD, relying on expert witnesses, such as Dr. Chung, whose views are more nuanced outside this litigation. But Plaintiffs certainly agree that genes play an important role in the development of these conditions. That is a point of common ground *despite* the fact that only a tiny fraction of “the precise” genes involved in triggering neurodevelopmental disorders are known. Dr. Chung offers her testimony nevertheless because scientists do not have to identify every relevant gene and observe it producing abnormalities to know that genes can cause abnormalities.

Defendants’ effort to play a levels-of-generality game on plausible biological mechanisms fails for the same reasons. The peer-reviewed literature is full of analysis assessing biological mechanisms that can cause ASD and ADHD without identifying the “precise pathogenesis” of the condition. Defendants’ excessively narrow view—that causal mechanisms cannot reliably be posited until every step of the causal pathway is definitively known—is clearly not shared by the scientific community, nor is it what Bradford Hill contemplated in his address.

For good reason. If an output is more frequently observed in the presence of a given input, one can conclude that the two are causally related without knowing exactly how the input yields the output. That much has been recognized since the *Daubert* litigation itself, where the Ninth Circuit explained on remand that “[n]ot knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff’s claim. Causation can be proved even when we don’t know precisely *how* the damage occurred, if there is sufficiently compelling proof that

the agent must have caused the damage *somehow*.” *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1314 (9th Cir. 1995).

Nevertheless, Dr. Pearson *does* chart the causal path from prenatal APAP exposure to ASD and ADHD through many identified mechanisms. The above summaries of those mechanisms provide only a fraction of the chemistry in Dr. Pearson’s thoroughly sourced report showing how APAP exposure causes certain chemical changes and how those changes can contribute to the development of ASD and ADHD. Throughout the report, Dr. Pearson provides graphics, several of which are explicitly labeled “pathways,” to help lay readers see the links in these causal chains. Take, for example, Figure 27, providing a “Graphical depiction of the ways oxidative stress can perturb neurodevelopment and lead to neurodevelopmental disorders,” which comes from a published study that is mentioned in none of Defendants’ briefs and which includes several disruptions—*e.g.*, brain inflammation, effects on DNA methylation, and mitochondrial dysfunction—leading specifically to ASD:

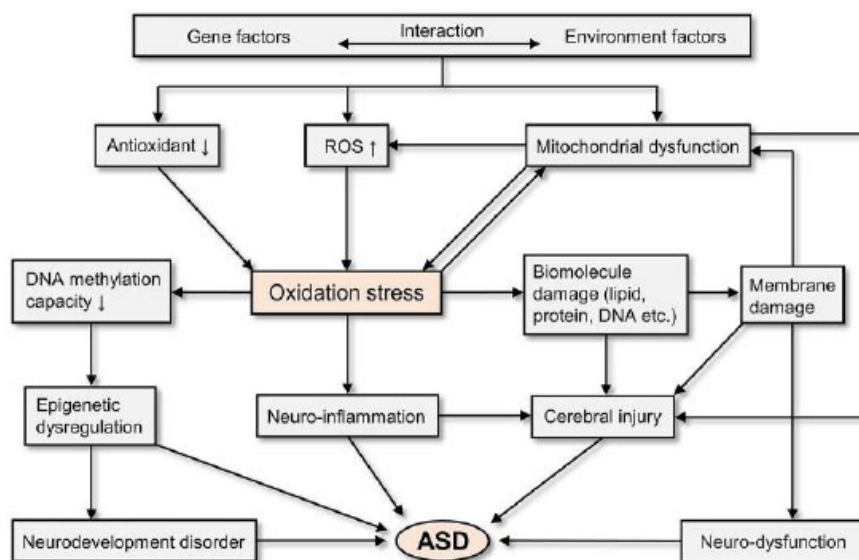


Figure 27. Graphical depiction of the ways oxidative stress can perturb neurodevelopment and lead to neurodevelopmental disorders.
Reproduced from Liu et al., 2022.

Ex. 2, Pearson Rep., at 52. Other pathway depictions in Dr. Pearson’s report include: Figure 16, showing how genetic and environmental factors affect the gene expressions and brain chemistry underlying the symptoms associated with ASD and ADHD, *see id.* at 32; Figure 28, showing “Pathways from APAP exposure to DNA damage,” *id.* at 55; Figure 31, showing “Multiple pathways for direct and indirect actions [of] APAP on fetal brain toxicity,” particularly through metabolism to NAPQI and depletion of glutathione, *id.* at 60; Figure 33, showing BDNF-related effects of prenatal APAP exposure in rats, *id.* at 63; and Figure 35, showing APAP effects on prostaglandins, as well as its effect on the endocannabinoid system through the creation of AM404, *id.* at 65. Defendants may attempt to contest that these are causal pathways. But Defendants cannot contest that they are laid out in Dr. Pearson’s report.

Defendants’ “corollary” argument—that Dr. Pearson’s conclusions are somehow unreliable because he identifies the same pathways for both ASD and ADHD—fails for the same reasons. Defs. Mech. Br. at 16. Defendants do not dispute the well-established premise that ASD and ADHD share a range of overlapping etiologies and symptoms that often co-occur. They certainly do not dispute that the same *genetic* factors are at work to cause both conditions. Nor do Defendants attempt to explain why a mechanism for one disorder could not be a mechanism for the other. Instead, this argument is an iteration of Defendants’ broader mischaracterization of Dr. Pearson’s report as “implicitly assuming” that any effect on brain development might lead to ASD or ADHD. *Id.* Since ASD and ADHD are the most common neurodevelopmental disorders and are defined by an array of abnormal behaviors resulting from a range of brain functions, it would be more plausible than not that toxic disruptions to neurodevelopment might lead to these disorders even if the same might not be true for a rarer disorder like Tourette’s syndrome. But

Dr. Pearson’s conclusions do not depend on that proposition. As just seen, his report illustrates in granular detail how the identified mechanisms can raise the risks of ASD and ADHD.

Defendants are therefore correct that Dr. Pearson’s report does not explain why “ASD and ADHD (and apparently every other type of neurodevelopmental deficit or disorder) would arise from a single cause,” because that is not a view expressed in his report. *Id.* at 17. Dr. Pearson shows how ASD and ADHD, in particular, result from the multiple cascading effects that APAP exposure has on neurodevelopment. By insisting on a single, specific pathway for these disorders, it is Defendants who fail to grapple with the variety of effects that prenatal APAP exposure can cause and from which ASD and ADHD can arise. As a result, they fail to address what Dr. Pearson’s report actually says.

B. Animal Models Provide Reliable Evidence of Causal Mechanisms.

Defendants next argue that, to the extent Plaintiffs’ expert opinions are based on animal studies, they are unreliable because Plaintiffs’ experts “fail to justify extrapolating from findings in rodents . . . to humans.” Defs. Mech. Br. at 14. This is not a serious argument. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

JJCI’s Senior Director of Epidemiology, Rachel Weinstein, similarly acknowledged at deposition that animal studies can provide relevant evidence of causation. *See* Ex. 88, Weinstein Dep. Tr. at 54:3–6 (“You certainly agree that animal models can be helpful in determining causation, correct? A. Yes.”). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] For JJCI, it appears that relevance depends on (supposed) result. The actual Rule 702 standard, unsurprisingly, is more even-handed. *See Daubert*, 509 U.S. at 595.

Of course, as Dr. Pearson readily admitted at deposition, rats and mice do not experience ASD and ADHD; these are human disorders. Latching onto that admission, Defendants assert that “it was incumbent on plaintiffs’ experts to justify extrapolating from findings in animal studies to any conclusion about ASD or ADHD in humans.” Defs. Mech. Br. at 15. Defendants conveniently missed that justification in Dr. Pearson’s report. In a long section of the report (which Defendants fail to cite, *see id.*), Dr. Pearson painstakingly explains how, with careful study design, rodent behaviors can model symptoms of ASD and ADHD and how biological changes in rodents can point to the mechanisms underlying those comparable behaviors. *See* Ex. 2, Pearson Rep., at 38–50. Scientists like Dr. Pearson live and breathe the challenges of translational science, and Dr. Pearson explicitly acknowledges and addresses the manner in which animal experiments relate to human populations both in his expert report and in his work outside of litigation.

Defendants’ only response is that rodent brains are smaller than human brains. *See* Defs. Mech. Br. at 15. That is a non sequitur. Biological responses in rodents are sufficiently similar to humans that scientists routinely conduct rodent studies to model ASD and ADHD. Defendants’ expert Dr. Powell is one of many scientists in that field who regularly uses mice to model autism in hopes of better understanding human manifestations of the disorder. *See* Ex. 30, Powell Dep.

Tr. at 33:10–17. Dr. Powell’s studies focus on genetics. But Defendants do not dispute that similar environmental exposures can also cause similar reactions in both species; [REDACTED]

[REDACTED] Animal models can provide reliable evidence that a toxicant can cause disorders through such interactions. And they are critically important when human studies would be unethical precisely because reasonable scientists are concerned about the adverse health outcomes the animal studies are evaluating.¹² *See also* Cabrera Opp’n at 22–25.

C. Findings Can Be Weighed Without Exact Replication.

Defendants also dismiss several preclinical findings on the ground that they have not been “replicated,” by which Defendants mean that the exact same tests have not been rerun to reach the exact same outcomes. Defendants do not locate this supposed replication requirement in any WoE guidance literature, because it does not exist. The WoE approach *assumes* some level of uncertainty in the existing data. *See* Ex. 141, OECD (2019), at 25 (“The acceptance and impact of uncertainty is a primary factor that influences all elements of WoE.”); *id.* at 18–19 (discussing “the integration of uncertainty into WoE”). Replication can bolster a finding, but it is often unrealistic for resource-intensive studies (as animal studies are), and findings do not need to be replicated to be weighed. The absence of the kind of certainty that can come from replication is why findings from disparate studies must be integrated and weighed in the first place.

Moreover, the studies lack strict “replication” because they tested for an array of potential effects of prenatal APAP exposure related to the development of ASD and ADHD. Rather than repetitively test one small set of interactions, “many studies have their own unique designs.” Ex. 7,

¹² John Talpos, the FDA’s Director of Neurotoxicology, also stated at the above-mentioned advisory board meeting that “[w]ithin the division we’re starting to research APAP-related neurotoxicity with vivo [animal] models.” Ex. 123, NCTR SAB Meeting (May 19, 2022), at 36. Query why JJCI is not commissioning such studies itself.

Pearson Rebuttal Rep., at 5–6. In fact, none of the studies that Dr. Pearson weighed attempted to redo the exact protocols of another. Such studies can nevertheless provide consistent evidence that prenatal APAP exposure is capable of causing relevant neurodevelopmental effects; that premise is again baked into the WoE approach to integrating evidence. *See* Ex. 141, OECD (2019), at 22–23. Indeed, the OECD guidance that Dr. Pearson followed, a [REDACTED] defines “consistency” as “the degree of consensus or corroboration among available data within a line of evidence”—and the example it provides is, simply, “developmental *effects*.” *Id.* at 18 (emphasis added). Thus, as Dr. Pearson explains, the “diversity” among studies “adds strength to overall weight of evidence—which shows that most studies find alterations to locomotion/activity, repetitive behavior, social behavior/communication, cognition, and neurochemistry in response to developmental APAP exposure.” Ex. 7, Pearson Rebuttal Rep., at 5–6. Weighing these findings is not cherry-picking. It is what a reliable WoE methodology requires.

D. Defendants’ Specific Responses to the Identified Mechanisms Are Baseless.

Finally, Defendants argue that some of the studies that Dr. Pearson reviewed do not support his conclusions about biological plausibility, primarily about the roles of NAPQI and oxidative stress. These arguments simply reflect and add to all the errors discussed above.

As an initial matter, Dr. Pearson does not opine that only “excessive *amounts* of acetaminophen, and therefore of NAPQI, can ‘deplete GSH [glutathione] levels,’” as Defendants suggest. Defs. Mech. Br. at 22 (emphasis added). His report explains that “prolonged or excessive *oxidative stress* can deplete GSH levels, leading to a compromised antioxidant defense system.” Ex. 2, Pearson Rep., at 52 (emphasis added). And his report shows that this “prolonged or excessive” state of imbalance can result from APAP taken at therapeutic doses; indeed, his report

explicitly excludes studies involving the “administration of APAP at levels well above therapeutic doses.” *Id.* at 69.

Defendants also appear to misunderstand Dr. Pearson’s opinion regarding glutathione, implying that he asserts that a certain amount of glutathione must be depleted for APAP to have toxic effects. That is not his opinion. As he explained, excess NAPQI requires excess glutathione to detoxify it, and the resulting depletion of this important antioxidant can be dangerous for neurodevelopment. *See* Ex. 2, Pearson Rep., at 58–59. But NAPQI itself can cause developmental injury even with antioxidants like glutathione present, because chronic exposure to a toxic reactive oxygen species, like NAPQI, is dangerous. Thus, while measurements of reduced glutathione can indicate the presence of NAPQI and oxidative stress, a particular level glutathione reduction is not required to conclude that APAP exposure might have toxic effects on neurodevelopment.

Defendants accordingly mistake the relevance of the Rigobello (2021) study. They argue that the study cannot show a causal association between prenatal APAP exposure and ASD/ADHD given that it found an effect on glutathione in mice at only a low dose of prenatal APAP exposure and not at higher doses. *See* Defs. Mech. Br. at 23–24. For the reasons just explained, toxicological conclusions can be drawn about the neurodevelopmental disorders modeled in those mice without a particular level of glutathione depletion. Moreover, glutathione is an endogenous antioxidant (produced in the body); higher levels of glutathione present at higher APAP doses could therefore reflect the body’s homeostatic response to the increased toxicant. In other words, cells in the body, in an attempt to maintain homeostasis in the face of a toxic chemical, are doing their best to respond and protect themselves from an environmental insult (*i.e.*, harm). *See supra* Background Part III.B (discussing homeostatic responses). The authors of the Anand 2021 study, which Defendants also mention, themselves acknowledge this compensatory glutathione response

to APAP-induced oxidative stress. *See* Ex. 142, Anand (2021), at 10. That study is unquestionably significant, as it locates a specific biomarker (a compound that results from oxidative stress) linking prenatal APAP exposure and ADHD. It thus provides a concrete example of the significant evidence that Defendants would exclude with their unscientific insistence on a single direction of all results in all studies, such as in glutathione levels. And in any event, Defendants acknowledge that even the Rigobello (2021) study found *an effect* from prenatal APAP exposure on glutathione levels, which is itself relevant. Dr. Pearson fully acknowledged the scope of that finding. *See* Ex. 2, Pearson Rep., at 96–97.

Defendants are similarly off the mark in their cursory responses to a few other studies related to oxidative stress and NAPQI.¹³ The Klein (2020) study found significant behavioral effects with no significant effect on LOOH (a measure of oxidative stress). But that alone is not evidence that APAP exposure did not cause those behavioral effects through oxidative stress: the study measured LOOH on postnatal-day 22, over three weeks after APAP exposure ceased. Thus, the oxidative damage and GSH effects could have been resolved by then, but the neurodevelopmental damage was already elicited, and the authors themselves note the potential link between one and the other. *See* Ex. 143, Klein (2020) at 6 (“Obviously, these data do not rule out the participation of oxidative stress in the developmental neurotoxicity induced by [APAP] since we have evaluated only one time point.”) (citation omitted). Defendants also argue that the Posadas (2010) study, titled *Acetaminophen Induces Apoptosis in Rat Cortical Neurons*, does not offer evidence that APAP induces apoptosis (cell death). Defendants simply misread this study,

¹³ Among their other scientific errors, Defendants assert that CYP2E1, the enzyme that metabolizes some APAP into NAPQI, is “almost absent from the brain.” Defs. Mech. Br. at 26. But its presence in the fetal brain is well-proven. *See* Ex. 2, Pearson Rep., at 18–20; *see also supra* Background Part II.B (quoting observation by the FDA’s Director of Neurotoxicology, John Talpos, that “[w]hile CYP2E1 is expressed on neurons in the human brain, it is at lower levels than in the liver, but it is still very much there”).

which was not performed on “adult rat cells in vitro,” but on embryonic cells, at doses below hepatotoxicity (liver toxicity). *See* Ex. 2, Pearson Rep., at 118–19. And this study is just one of the pieces of evidence that Dr. Pearson provides of NAPQI’s role in apoptosis and of its other directly toxic effects on neurodevelopment. *See id.* at 58–60.

That leaves the Saeedan (2018) study, one of the studies that Defendants erroneously describe as failing to correct for multiple comparisons. *See supra* Argument Part II.B. Curiously, Defendants assert that this study “fails to support [Plaintiffs’] theory” even while explicitly acknowledging that the rats exposed to doses of APAP equivalent prenatal exposure at therapeutic human doses “showed significant reductions in GSH [glutathione]” as well as “significant increases in TABRs, a marker of oxidative stress.” Defs. Mech. Br. at 24. Defendants note that “so too did rats given vaccines,” including the measles and tetanus vaccines, *id.*, and they suggest that recognizing this study as additional evidence of prenatal APAP exposure’s contribution to ASD and ADHD would therefore be equivalent to the “conspiracy theory” that vaccines contribute to ASD, *id.* at 24 n.16. The equivalence is false. These vaccines are not administered on fetuses. Any findings or theories about vaccines given to children after birth have nothing to do with the harms alleged here.

Defendants take further swipes at a few studies underlying the several other mechanisms shown in Dr. Pearson’s report. These are only more premature previews of their merits arguments. They are also meritless. As to endocannabinoid disruptions,¹⁴ Defendants assert that Dr. Pearson provides “a one-sided and misleading summary” of Klein (2023), Defs. Mech. Br. at 30, in which

¹⁴ Defendants make only passing reference to Dr. Pearson’s discussion of epigenetic changes, saying that he “makes no real effort to link the concept to either acetaminophen or ASD and ADHD.” Defs.’ Mech. Br. at 32 n.39. Dr. Pearson considered the relevant studies, including on DNA methylation; his report has a section on epigenetic changes, *see* Ex. 2, Pearson Rep., at 60–61; and as seen above, he diagrams the pathways by which gene-environment interactions can lead to ASD, including through “[e]pigenetic dysregulation,” *id.* at 52 fig.27.

the authors concluded that “[endocannabinoid] dysfunction may play a role in the action by which [APAP] may harm the developing brain.” Ex. 144, Klein (2023), at 1. Defendants interpret some findings within this study to weigh against endocannabinoid effects as a mechanism. Those interpretations are themselves debatable, but Defendants cannot avoid the study’s other findings that APAP does act on neurodevelopment through the endocannabinoid system. More importantly for present purposes, Dr. Pearson acknowledges the study’s range of findings, as does Dr. Cabrera. *See* Ex. 11, Pearson Supp. Report, at 3; Ex. 12, Cabrera Supp. Report, at 1–3. Defendants, meanwhile, cite no scientific support for their speculation that changes to the endocannabinoid system are somehow “just as likely to result from ASD or ADHD as to cause it.” Defs. Mech. Br. at 31. Nor can this speculation address the evidence linking prenatal APAP exposure to endocannabinoid changes and to ASD and ADHD.

Defendants’ remaining responses are more cursory still. On serotonin and BDNF, they continue to demand a change in a particular direction despite evidence showing that abnormalities in either system can itself be a risk factor for ASD or ADHD. They even try to criticize Dr. Pearson for failing to “harmonize” a study showing APAP’s impact on BDNF with a study that did not measure BDNF. Defs. Mech. Br. 36 & n.54 (citing Ex. 136, Blecharz-Klin (2017)). And they again speculate that abnormal serotonergic functioning might result from rather than cause these disorders, again without support. Finally, Defendants admit that APAP “almost certainly does inhibit prostaglandin synthesis,” *id.* at 37 n.56, yet they dismiss “any link between that fact and ASD or ADHD” as “pure speculation,” *id.* at 38, without addressing the multiple links that Dr. Pearson draws between that fact and ASD and ADHD. *See* Ex. 2, Pearson Rep., at 65–66, 84–85.

But it bears repeating: these are all disputes for after the *Daubert* phase. Defendants’ preemptive, substantive attacks on the evidence underlying Dr. Pearson’s conclusions are not just

scientifically incorrect. They also refute the premise of Defendants' *Daubert* motion [REDACTED]

[REDACTED]. But the place to do that is at trial, not in a *Daubert* brief. Dr. Pearson is qualified to weigh the same evidence and reach a different conclusion. He has reliably done so.

CONCLUSION

For the foregoing reasons, the Court should deny Defendants' Rule 702 Motions to Exclude Dr. Pearson.

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